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Species-specific differences in peroxisome proliferation, catalase, and SOD2 upregulation as well as toxicity in human, mouse, and rat hepatoma cells induced by the explosive and environmental pollutant 2,4,6-trinitrotoluene

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Abstract

© 2016 Wiley Periodicals, Inc. 2,4,6-Trinitrotoluene (TNT) has been widely used as an explosive substance and its toxicity is still of interest as it persisted in polluted areas. TNT is metabolized in hepatocytes which are prone to its toxicity. Since analysis of the human liver or hepatocytes is restricted due to ethical reasons, we investigated the effects of TNT on cell viability, reactive oxygen species (ROS) production, peroxisome proliferation, and antioxidative enzymes in human (HepG2), mouse (Hepa 1-6), and rat (H4IIEC3) hepatoma cell lines. Under control conditions, hepatoma cells of all three species were highly comparable exhibiting identical proliferation rates and distribution of their cell cycle phases. However, we found strong differences in TNT toxicity with the lowest IC 50 values (highest cell death rate) for rat cells, whereas human and mouse cells were three to sevenfold less sensitive. Moreover, a strong decrease in cellular dehydrogenase activity (MTT assay) and increased ROS levels were noted. TNT caused peroxisome proliferation with rat hepatoma cells being most responsive followed by those from mouse and human. Under control conditions, rat cells contained fivefold higher peroxisomal catalase and mitochondrial SOD2 activities and a twofold higher capacity to reduce MTT than human and mouse cells. TNT treatment caused an increase in catalase and SOD2 mRNA and protein levels in human and mouse, but not in rat cells. Similarly, human and mouse cells upregulated SOD2 activity, whereas rat cells failed therein. We conclude that TNT induced oxidative stress, peroxisome proliferation and mitochondrial damage which are highest in rat cells rendering them most susceptibl e toward TNT. © 2016 Wiley Periodicals, Inc. Environ Toxicol 32: 989–1006, 2017.

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Keywords

catalase, hepatoma cells, human, mouse, peroxisome proliferation, PEX14, rat, SOD2, superoxide radical anion, TNT

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